

Amendments to the Specification:

Please delete the paragraph beginning at page 1, paragraph [001] and replace with the following rewritten paragraph:

--[001] This application is a continuation-in-part of USSN 10/672,280, filed September 26, 2003 which claims benefit under 35 U.S.C. §199(e) 119(e) to USSNs 10/672,280, filed September 26, 2003, 10/379,392, filed March 3, 2003, 60/477,839 filed June 12, 2003; 60/467,606, filed May 2, 2003; 60/414,433 filed September 27, 2002; and 60/442,301 filed January 23, 2003, and is a continuation-in-part of USSN 10/379,392, filed March 3, 2003, all of which are expressly incorporated by reference in their entirety.--

Please delete the paragraph beginning at page 19, paragraph [039] and replace with the following rewritten paragraph:

--[039] Figure 3. The amino acid sequence of the heavy chain of the antibody alemtuzumab (Campath®, a registered trademark of Ilex Pharmaceuticals LP) (SEQ ID NO:1), illustrating positions numbered sequentially (2 lines above the amino acid sequence) and positions numbered according to the EU index as in Kabat (2 lines below the amino acid sequence. The approximate beginnings of Ig domains VH1, Cy1, the hinge, Cy2, and Cy3 are also labeled above the sequential numbering. Polymorphisms have been observed at a number of Fc positions, including but not limited to Kabat 270, 272, 312, 315, 356, and 358, and thus slight differences between the presented sequence and sequences in the prior art may exist.-

Please delete the paragraph beginning at page 19, paragraph [041] and replace with the following rewritten paragraph:

--[041] Figure 5. The human IgG1 Fc sequence (SEQ ID NO:2) showing positions relevant to the design of the Fc variant experimental library. The sequence includes the hinge region, domain Cy2, and domain Cy3. Residue numbers are according to the EU index as in Kabat. Positions relevant to the experimental library are underlined. Because of observed polymorphic mutations at a number of Fc positions, slight differences between the presented sequence and sequences in the literature may exist.--

Please delete the paragraph beginning at page 25, paragraph [074] and replace with the following rewritten paragraph:

-- [074] Figures 38a – 38c. Sequences showing improved anti-CD20 antibodies. The light and heavy chain sequences of rituximab (SEQ ID NOs:3 and 4) are presented in Figure 38a and Figure 38b respectively, and are taken from translated Sequence 3 of US 5,736,137. Relevant positions in Figure

38b are bolded, including S239, V240, V264I, E272, K274, N297, S298, K326, A330, and I332. Figure 38c shows the improved anti-CD20 antibody heavy chain sequences, with variable positions designated in bold as X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈, Z₁, and Z₂ (SEQ ID NO:5). The table below the sequence provides possible substitutions for these positions. The improved anti-CD20 antibody sequences comprise at least one non-WT amino acid selected from the group of possible substitutions for X₁, X₂, X₃, X₄, X₅, X₆, X₇, and X₈. These improved anti-CD20 antibody sequences may also comprise a substitution Z₁ and/or Z₂. These positions are numbered according to the EU index as in Kabat, and thus do not correspond to the sequential order in the sequence. --

Please delete the paragraph beginning at page 45, paragraph [0118] and replace with the following rewritten paragraph:

--[118] A variety of linkers may find use in the present invention to generate Fc fusions (see definition above) or antibody- or Fc fusion- conjugates (see definition below). By “linker”, “linker sequence”, “spacer”, “tethering sequence” or grammatical equivalents thereof, herein is meant a molecule or group of molecules (such as a monomer or polymer) that connects two molecules and often serves to place the two molecules in a preferred configuration. A number of strategies may be used to covalently link molecules together. These include, but are not limited to polypeptide linkages between N- and C-termini of proteins or protein domains, linkage via disulfide bonds, and linkage via chemical cross-linking reagents. In one aspect of this embodiment, the linker is a peptide bond, generated by recombinant techniques or peptide synthesis. Choosing a suitable linker for a specific case where two polypeptide chains are to be connected depends on various parameters, including but not limited to the nature of the two polypeptide chains (e.g., whether they naturally oligomerize), the distance between the N- and the C-termini to be connected if known, and/or the stability of the linker towards proteolysis and oxidation. Furthermore, the linker may contain amino acid residues that provide flexibility. Thus, the linker peptide may predominantly include the following amino acid residues: Gly, Ser, Ala, or Thr. The linker peptide should have a length that is adequate to link two molecules in such a way that they assume the correct conformation relative to one another so that they retain the desired activity. Suitable lengths for this purpose include at least one and not more than 30 amino acid residues. Preferably, the linker is from about 1 to 30 amino acids in length, with linkers of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 19 and 20 amino acids in length being preferred. In addition, the amino acid residues selected for inclusion in the linker peptide should exhibit properties that do not interfere significantly with the activity of the polypeptide. Thus, the linker peptide on the whole should not exhibit a charge that would be inconsistent with the activity of the polypeptide, or interfere with internal folding, or form bonds or other interactions with amino acid

residues in one or more of the monomers that would seriously impede the binding of receptor monomer domains. Useful linkers include glycine-serine polymers (including, for example, (GS)_n, (GSGGS)_n (SEQ ID NO:6), (GGGGS)_n (SEQ ID NO:7) and (GGGS)_n (SEQ ID NO:8), where n is an integer of at least one), glycine-alanine polymers, alanine-serine polymers, and other flexible linkers such as the tether for the shaker potassium channel, and a large variety of other flexible linkers, as will be appreciated by those in the art. Glycine-serine polymers are preferred since both of these amino acids are relatively unstructured, and therefore may be able to serve as a neutral tether between components. Secondly, serine is hydrophilic and therefore able to solubilize what could be a globular glycine chain. Third, similar chains have been shown to be effective in joining subunits of recombinant proteins such as single chain antibodies. Suitable linkers may also be identified by screening databases of known three-dimensional structures for naturally occurring motifs that can bridge the gap between two polypeptide chains. In a preferred embodiment, the linker is not immunogenic when administered in a human patient. Thus linkers may be chosen such that they have low immunogenicity or are thought to have low immunogenicity. For example, a linker may be chosen that exists naturally in a human. In a preferred embodiment the linker has the sequence of the hinge region of an antibody, that is the sequence that links the antibody Fab and Fc regions; alternatively the linker has a sequence that comprises part of the hinge region, or a sequence that is substantially similar to the hinge region of an antibody. Another way of obtaining a suitable linker is by optimizing a simple linker, e.g., (Gly₄Ser)_n, through random mutagenesis. Alternatively, once a suitable polypeptide linker is defined, additional linker polypeptides can be created to select amino acids that more optimally interact with the domains being linked. Other types of linkers that may be used in the present invention include artificial polypeptide linkers and inteins. In another embodiment, disulfide bonds are designed to link the two molecules. In another embodiment, linkers are chemical cross-linking agents. For example, a variety of bifunctional protein coupling agents may be used, including but not limited to N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate, iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., 1971, Science 238:1098. Chemical linkers may enable chelation of an isotope. For example, Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody (see PCT WO 94/11026).

The linker may be cleavable, facilitating release of the cytotoxic drug in the cell. For example, an acid-labile linker, peptidase-sensitive linker, dimethyl linker or disulfide-containing linker (Chari et al., 1992, Cancer Research 52: 127-131) may be used. Alternatively, a variety of nonproteinaceous polymers, including but not limited to polyethylene glycol (PEG), polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol and polypropylene glycol, may find use as linkers, that is may find use to link the Fc variants of the present invention to a fusion partner to generate an Fc fusion, or to link the antibodies and Fc fusions of the present invention to a conjugate.--

Please delete the paragraph beginning at page 73, paragraph [050] and replace with the following rewritten paragraph:

--[176] Fc variants may be operably linked to a fusion partner to enable targeting of the expressed protein, purification, screening, display, and the like. Fusion partners may be linked to the Fc variant sequence via a linker sequences. The linker sequence will generally comprise a small number of amino acids, typically less than ten, although longer linkers may also be used. Typically, linker sequences are selected to be flexible and resistant to degradation. As will be appreciated by those skilled in the art, any of a wide variety of sequences may be used as linkers. For example, a common linker sequence comprises the amino acid sequence GGGGS (SEQ ID NO:7). A fusion partner may be a targeting or signal sequence that directs Fc variant protein and any associated fusion partners to a desired cellular location or to the extracellular media. As is known in the art, certain signaling sequences may target a protein to be either secreted into the growth media, or into the periplasmic space, located between the inner and outer membrane of the cell. A fusion partner may also be a sequence that encodes a peptide or protein that enables purification and/or screening. Such fusion partners include but are not limited to polyhistidine tags (His-tags) (for example H₆ and H₁₀ or other tags for use with Immobilized Metal Affinity Chromatography (IMAC) systems (e.g. Ni⁺² affinity columns)), GST fusions, MBP fusions, Strep-tag, the BSP biotinylation target sequence of the bacterial enzyme BirA, and epitope tags which are targeted by antibodies (for example c-myc tags, flag-tags, and the like). As will be appreciated by those skilled in the art, such tags may be useful for purification, for screening, or both. For example, an Fc variant may be purified using a His-tag by immobilizing it to a Ni⁺² affinity column, and then after purification the same His-tag may be used to immobilize the antibody to a Ni⁺² coated plate to perform an ELISA or other binding assay (as described below). A fusion partner may enable the use of a selection method to screen Fc variants (see below). Fusion partners that enable a variety of selection methods are well-known in the art, and all of these find use in the present invention. For example, by fusing the members of an Fc variant library to the gene III protein, phage display can be employed (Kay *et al.*,

Phage display of peptides and proteins: a laboratory manual, Academic Press, San Diego, CA, 1996; Lowman *et al.*, 1991, *Biochemistry* 30:10832-10838; Smith, 1985, *Science* 228:1315-1317). Fusion partners may enable Fc variants to be labeled. Alternatively, a fusion partner may bind to a specific sequence on the expression vector, enabling the fusion partner and associated Fc variant to be linked covalently or noncovalently with the nucleic acid that encodes them. For example, USSN 09/642,574; USSN 10/080,376; USSN 09/792,630; USSN 10/023,208; USSN 09/792,626; USSN 10/082,671; USSN 09/953,351; USSN 10/097,100; USSN 60/366,658; PCT WO 00/22906; PCT WO 01/49058; PCT WO 02/04852; PCT WO 02/04853; PCT WO 02/08023; PCT WO 01/28702; and PCT WO 02/07466 describe such a fusion partner and technique that may find use in the present invention.--

Please delete page 89 since it is a blank page.

Please delete the paragraph beginning at page 120, paragraph [204] and replace with the following rewritten paragraph:

--[204] The results of the design calculations presented above in Tables 1 – 60 were used to construct a series of Fc variant libraries for experimental production and screening. Experimental libraries were designed in successive rounds of computational and experimental screening. Design of subsequent Fc libraries benefitted from feedback from prior libraries, and thus typically comprised combinations of Fc variants that showed favorable properties in the previous screen. The entire set of Fc variants that were constructed and experimentally tested is shown in Table 61. In this table, row 1 lists the variable positions, and the rows that follow indicate the amino acids at those variable positions for WT and the Fc variants. For example, variant 18 (SEQ ID NO:26) has the following four mutations: F241E, F243Y, V262T, and V264R. The variable position residues that compose this set of Fc variants are illustrated structurally in Figure 4, and are presented in the context of the human IgG1 Fc sequence (SEQ ID NO:2) in Figure 5.--

Please delete Table 61 beginning at page 121 and replace with the following rewritten table:

Table 61

Variant	SEQ ID NO	Substitution(s)	Variant	SEQ ID NO	Substitution(s)
1	SEQ ID NO:9	V264A	50	SEQ ID NO:55	Y296Q
2	SEQ ID NO:10	V264L	51	SEQ ID NO:56	S298T
3	SEQ ID NO:11	V264I	52	SEQ ID NO:57	S298N
4	SEQ ID NO:12	F241W	53	SEQ ID NO:58	T299I
5	SEQ ID NO:13	F241L	54	SEQ ID NO:59	A327S
6	SEQ ID NO:14	F243W	55	SEQ ID NO:60	A327N
7	SEQ ID NO:15	F243L	56	SEQ ID NO:61	S267Q/A327S

Serial No.: 10/822,231
Filing Date: March 26, 2004

8	SEQ ID NO:16	F241L/F243L/V262I/V264I	57	SEQ ID NO:62	S267L/A327S
9	SEQ ID NO:17	F241W/F243W	58	SEQ ID NO:63	A327L
10	SEQ ID NO:18	F241W/F243W/V262A/V264A	59	SEQ ID NO:64	P329F
11	SEQ ID NO:19	F241L/V262I	60	SEQ ID NO:65	A330L
12	SEQ ID NO:20	F243L/V264I	61	SEQ ID NO:66	A330Y
13	SEQ ID NO:21	F243L/V262I/V264W	62	SEQ ID NO:67	I332D
14	SEQ ID NO:22	F241Y/F243Y/V262T/V264T	63	SEQ ID NO:68	N297S
15	SEQ ID NO:23	F241E/F243R/V262E/V264R	64	SEQ ID NO:69	N297D
16	SEQ ID NO:24	F241E/F243Q/V262T/V264E	65	SEQ ID NO:70	N297S/I332E
17	SEQ ID NO:25	F241R/F243Q/V262T/V264R	66	SEQ ID NO:71	N297D/I332E
18	SEQ ID NO:26	F241E/F243Y/V262T/V264R	67	SEQ ID NO:72	N297E/I332E
19	SEQ ID NO:27	L328M	68	SEQ ID NO:73	D265Y/N297D/I332E
20	SEQ ID NO:28	L328E	69	SEQ ID NO:74	D265Y/N297D/T299L/I332E
21	SEQ ID NO:29	L328F	70	SEQ ID NO:75	D265F/N297E/I332E
22	SEQ ID NO:30	I332E	71	SEQ ID NO:76	L328I/I332E
23	SEQ ID NO:31	L328M/I332E	72	SEQ ID NO:77	L328Q/I332E
24	SEQ ID NO:32	P244H	73	SEQ ID NO:78	I332N
25	SEQ ID NO:33	P245A	74	SEQ ID NO:79	I332Q
26	SEQ ID NO:34	P247V	75	SEQ ID NO:80	V264T
27	SEQ ID NO:35	W313F	76	SEQ ID NO:81	V264F
28	SEQ ID NO:36	P244H/P245A/P247V	77	SEQ ID NO:82	V240I
29	SEQ ID NO:37	P247G	78	SEQ ID NO:83	V263I
30	SEQ ID NO:38	V264I/I332E	79	SEQ ID NO:84	V266I
31	SEQ ID NO:39	F241E/F243R/V262E/V264R/I332E	80	SEQ ID NO:85	T299A
32	SEQ ID NO:40	F241E/F243Q/V262T/V264E/I332E	81	SEQ ID NO:86	T299S
33	SEQ ID NO:41	F241R/F243Q/V262T/V264R/I332E	82	SEQ ID NO:87	T299V
34	SEQ ID NO:42	F241E/F243Y/V262T/V264R/I332E	83	SEQ ID NO:88	N325Q
35	SEQ ID NO:43	S298A	84	SEQ ID NO:89	N325L
36	SEQ ID NO:44	S298A/I332E	85	SEQ ID NO:90	N325I
37	SEQ ID NO:45	S298A/E333A/K334A	86	SEQ ID NO:91	S239D
41	SEQ ID NO:46	S239E/I332E	87	SEQ ID NO:92	S239N
42	SEQ ID NO:47	S239Q/I332E	88	SEQ ID NO:93	S239F
43	SEQ ID NO:48	S239E	89	SEQ ID NO:94	S239D/I332D
44	SEQ ID NO:49	D265G	90	SEQ ID NO:95	S239D/I332E
45	SEQ ID NO:50	D265N	91	SEQ ID NO:96	S239D/I332N
46	SEQ ID NO:51	S239E/D265G	92	SEQ ID NO:97	S239D/I332Q
47	SEQ ID NO:52	S239E/D265N	93	SEQ ID NO:98	S239E/I332D
48	SEQ ID NO:53	S239E/D265Q	94	SEQ ID NO:99	S239E/I332N
49	SEQ ID NO:54	Y296E	95	SEQ ID NO:100	S239E/I332Q

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Please delete Table 61 (continued) beginning at page 122 and replace with the following rewritten table:

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Table 61 (continued)

Variant	SEQ ID NO	Substitution(s)	Variant	SEQ ID NO	Substitution(s)
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Serial No.: 10/822,231
Filing Date: March 26, 2004

96	<u>SEQ ID NO:101</u>	S239N/I332D	141	<u>SEQ ID NO:146</u>	V264Y
97	<u>SEQ ID NO:102</u>	S239N/I332E	142	<u>SEQ ID NO:147</u>	V266A
98	<u>SEQ ID NO:103</u>	S239N/I332N	143	<u>SEQ ID NO:148</u>	V266T
99	<u>SEQ ID NO:104</u>	S239N/I332Q	144	<u>SEQ ID NO:149</u>	V266M
100	<u>SEQ ID NO:105</u>	S239Q/I332D	145	<u>SEQ ID NO:150</u>	E269H
101	<u>SEQ ID NO:106</u>	S239Q/I332N	146	<u>SEQ ID NO:151</u>	E269Y
102	<u>SEQ ID NO:107</u>	S239Q/I332Q	147	<u>SEQ ID NO:152</u>	E269F
103	<u>SEQ ID NO:108</u>	K326E	148	<u>SEQ ID NO:153</u>	E269R
104	<u>SEQ ID NO:109</u>	Y296D	149	<u>SEQ ID NO:154</u>	Y296S
105	<u>SEQ ID NO:110</u>	Y296N	150	<u>SEQ ID NO:155</u>	Y296T
106	<u>SEQ ID NO:111</u>	N297D/I332E/F241Y/F243Y/V262T/V264T	151	<u>SEQ ID NO:156</u>	Y296L
107	<u>SEQ ID NO:112</u>	I332E/A330Y	152	<u>SEQ ID NO:157</u>	Y296I
108	<u>SEQ ID NO:113</u>	I332E/V264I/A330Y	153	<u>SEQ ID NO:158</u>	S298H
109	<u>SEQ ID NO:114</u>	I332E/A330L	154	<u>SEQ ID NO:159</u>	T299H
110	<u>SEQ ID NO:115</u>	I332E/V264I/A330L	155	<u>SEQ ID NO:160</u>	A330V
111	<u>SEQ ID NO:116</u>	L234D	156	<u>SEQ ID NO:161</u>	A330I
112	<u>SEQ ID NO:117</u>	L234E	157	<u>SEQ ID NO:162</u>	A330F
113	<u>SEQ ID NO:118</u>	L234N	158	<u>SEQ ID NO:163</u>	A330R
114	<u>SEQ ID NO:119</u>	L234Q	159	<u>SEQ ID NO:164</u>	A330H
115	<u>SEQ ID NO:120</u>	L234T	160	<u>SEQ ID NO:165</u>	N325D
116	<u>SEQ ID NO:121</u>	L234H	161	<u>SEQ ID NO:166</u>	N325E
117	<u>SEQ ID NO:122</u>	L234Y	162	<u>SEQ ID NO:167</u>	N325A
118	<u>SEQ ID NO:123</u>	L234I	163	<u>SEQ ID NO:168</u>	N325T
119	<u>SEQ ID NO:124</u>	L234V	164	<u>SEQ ID NO:169</u>	N325V
120	<u>SEQ ID NO:125</u>	L234F	165	<u>SEQ ID NO:170</u>	N325H
121	<u>SEQ ID NO:126</u>	L235D	166	<u>SEQ ID NO:171</u>	L328D/I332E
122	<u>SEQ ID NO:127</u>	L235S	167	<u>SEQ ID NO:172</u>	L328E/I332E
123	<u>SEQ ID NO:128</u>	L235N	168	<u>SEQ ID NO:173</u>	L328N/I332E
124	<u>SEQ ID NO:129</u>	L235Q	169	<u>SEQ ID NO:174</u>	L328Q/I332E
125	<u>SEQ ID NO:130</u>	L235T	170	<u>SEQ ID NO:175</u>	L328V/I332E
126	<u>SEQ ID NO:131</u>	L235H	171	<u>SEQ ID NO:176</u>	L328T/I332E
127	<u>SEQ ID NO:132</u>	L235Y	172	<u>SEQ ID NO:177</u>	L328H/I332E
128	<u>SEQ ID NO:133</u>	L235I	173	<u>SEQ ID NO:178</u>	L328I/I332E
129	<u>SEQ ID NO:134</u>	L235V	174	<u>SEQ ID NO:179</u>	L328A
130	<u>SEQ ID NO:135</u>	L235F	175	<u>SEQ ID NO:180</u>	I332T
131	<u>SEQ ID NO:136</u>	S239T	176	<u>SEQ ID NO:181</u>	I332H
132	<u>SEQ ID NO:137</u>	S239H	177	<u>SEQ ID NO:182</u>	I332Y
133	<u>SEQ ID NO:138</u>	S239Y	178	<u>SEQ ID NO:183</u>	I332A
134	<u>SEQ ID NO:139</u>	V240A	179	<u>SEQ ID NO:184</u>	V264I/I332E/S239E
135	<u>SEQ ID NO:140</u>	V240T	180	<u>SEQ ID NO:185</u>	V264I/I332E/S239Q
136	<u>SEQ ID NO:141</u>	V240M	181	<u>SEQ ID NO:186</u>	V264I/I332E/S239E/A330Y
137	<u>SEQ ID NO:142</u>	V263A	182	<u>SEQ ID NO:187</u>	V264I/I332E/S239E/A330Y/S298A
138	<u>SEQ ID NO:143</u>	V263T	183	<u>SEQ ID NO:188</u>	N297D/I332E/S239D
139	<u>SEQ ID NO:144</u>	V263M	184	<u>SEQ ID NO:189</u>	N297D/I332E/S239E
140	<u>SEQ ID NO:145</u>	V264M	185	<u>SEQ ID NO:190</u>	N297D/I332E/S239D/D265V

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Please delete Table 61 (continued) beginning at page 123 and replace with the following rewritten table:

-- Table 61 (continued)

Variant	SEQ ID NO	Substitution(s)	Variant	SEQ ID NO	Substitution(s)
186	<u>SEQ ID NO:191</u>	N297D/I332E/S239D/D265I	231	<u>SEQ ID NO:236</u>	E269N
187	<u>SEQ ID NO:192</u>	N297D/I332E/S239D/D265L	232	<u>SEQ ID NO:237</u>	D270Q
188	<u>SEQ ID NO:193</u>	N297D/I332E/S239D/D265F	233	<u>SEQ ID NO:238</u>	D270T
189	<u>SEQ ID NO:194</u>	N297D/I332E/S239D/D265Y	234	<u>SEQ ID NO:239</u>	D270H
190	<u>SEQ ID NO:195</u>	N297D/I332E/S239D/D265H	235	<u>SEQ ID NO:240</u>	E272S
191	<u>SEQ ID NO:196</u>	N297D/I332E/S239D/D265T	236	<u>SEQ ID NO:241</u>	E272K
192	<u>SEQ ID NO:197</u>	N297D/I332E/V264E	237	<u>SEQ ID NO:242</u>	E272I
193	<u>SEQ ID NO:198</u>	N297D/I332E/Y296D	238	<u>SEQ ID NO:243</u>	E272Y
194	<u>SEQ ID NO:199</u>	N297D/I332E/Y296E	239	<u>SEQ ID NO:244</u>	V273I
195	<u>SEQ ID NO:200</u>	N297D/I332E/Y296N	240	<u>SEQ ID NO:245</u>	K274T
196	<u>SEQ ID NO:201</u>	N297D/I332E/Y296Q	241	<u>SEQ ID NO:246</u>	K274E
197	<u>SEQ ID NO:202</u>	N297D/I332E/Y296H	242	<u>SEQ ID NO:247</u>	K274R
198	<u>SEQ ID NO:203</u>	N297D/I332E/Y296T	243	<u>SEQ ID NO:248</u>	K274L
199	<u>SEQ ID NO:204</u>	N297D/I332E/T299V	244	<u>SEQ ID NO:249</u>	K274Y
200	<u>SEQ ID NO:205</u>	N297D/I332E/T299I	245	<u>SEQ ID NO:250</u>	F275W
201	<u>SEQ ID NO:206</u>	N297D/I332E/T299L	246	<u>SEQ ID NO:251</u>	N276S
202	<u>SEQ ID NO:207</u>	N297D/I332E/T299F	247	<u>SEQ ID NO:252</u>	N276E
203	<u>SEQ ID NO:208</u>	N297D/I332E/T299H	248	<u>SEQ ID NO:253</u>	N276R
204	<u>SEQ ID NO:209</u>	N297D/I332E/T299E	249	<u>SEQ ID NO:254</u>	N276L
205	<u>SEQ ID NO:210</u>	N297D/I332E/A330Y	250	<u>SEQ ID NO:255</u>	N276Y
206	<u>SEQ ID NO:211</u>	N297D/I332E/S298A/A330Y	251	<u>SEQ ID NO:256</u>	Y278T
207	<u>SEQ ID NO:212</u>	S239D/I332E/A330Y	252	<u>SEQ ID NO:257</u>	Y278E
208	<u>SEQ ID NO:213</u>	S239N/I332E/A330Y	253	<u>SEQ ID NO:258</u>	Y278K
209	<u>SEQ ID NO:214</u>	S239D/I332E/A330L	254	<u>SEQ ID NO:259</u>	Y278W
210	<u>SEQ ID NO:215</u>	S239N/I332E/A330L	255	<u>SEQ ID NO:260</u>	E283R
211	<u>SEQ ID NO:216</u>	I332E/V264I/S298A	256	<u>SEQ ID NO:261</u>	V302I
212	<u>SEQ ID NO:217</u>	I332E/S239D/S298A	257	<u>SEQ ID NO:262</u>	E318R
213	<u>SEQ ID NO:218</u>	I332E/S239N/S298A	258	<u>SEQ ID NO:263</u>	K320T
214	<u>SEQ ID NO:219</u>	S239D/I332E/V264I	259	<u>SEQ ID NO:264</u>	K320D
215	<u>SEQ ID NO:220</u>	S239D/I332E/V264I/S298A	260	<u>SEQ ID NO:265</u>	K320I
216	<u>SEQ ID NO:221</u>	S239D/I332E/V264I/A330L	261	<u>SEQ ID NO:266</u>	K322T
217	<u>SEQ ID NO:222</u>	L328N	262	<u>SEQ ID NO:267</u>	K322H
218	<u>SEQ ID NO:223</u>	L328H	263	<u>SEQ ID NO:268</u>	V323I
219	<u>SEQ ID NO:224</u>	S239D/I332E/A330I	264	<u>SEQ ID NO:269</u>	S324T
220	<u>SEQ ID NO:225</u>	N297D/I332E/S239D/A330L	265	<u>SEQ ID NO:270</u>	S324D
221	<u>SEQ ID NO:226</u>	P230A	266	<u>SEQ ID NO:271</u>	S324R
222	<u>SEQ ID NO:227</u>	E233D	267	<u>SEQ ID NO:272</u>	S324I
223	<u>SEQ ID NO:228</u>	P230A/E233D	268	<u>SEQ ID NO:273</u>	S324V
224	<u>SEQ ID NO:229</u>	P230A/E233D/I332E	269	<u>SEQ ID NO:274</u>	S324L
225	<u>SEQ ID NO:230</u>	S267T	270	<u>SEQ ID NO:275</u>	S324Y
226	<u>SEQ ID NO:231</u>	S267H	271	<u>SEQ ID NO:276</u>	K326L
227	<u>SEQ ID NO:232</u>	S267D	272	<u>SEQ ID NO:277</u>	K326I
228	<u>SEQ ID NO:233</u>	S267N	273	<u>SEQ ID NO:278</u>	K326T
229	<u>SEQ ID NO:234</u>	E269T	274	<u>SEQ ID NO:279</u>	A327D

230	SEQ ID NO:235	E269L	275	SEQ ID NO:280	A327T
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Please delete Table 61 (continued) beginning at page 124 and replace with the following rewritten table:

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Table 61 (continued)

Variant	SEQ ID NO	Substitution(s)	Variant	SEQ ID NO	Substitution(s)
276	SEQ ID NO:281	A330S	290	SEQ ID NO:295	T335Y
277	SEQ ID NO:282	A330W	291	SEQ ID NO:296	L234I/L235D
278	SEQ ID NO:283	A330M	292	SEQ ID NO:297	V240I/V266I
279	SEQ ID NO:284	P331V	293	SEQ ID NO:298	S239D/A330Y/I332E/L234I
280	SEQ ID NO:285	P331H	294	SEQ ID NO:299	S239D/A330Y/I332E/L235D
281	SEQ ID NO:286	E333T	295	SEQ ID NO:300	S239D/A330Y/I332E/V240I
282	SEQ ID NO:287	E333H	296	SEQ ID NO:301	S239D/A330Y/I332E/V264T
283	SEQ ID NO:288	E333I	297	SEQ ID NO:302	S239D/A330Y/I332E/V266I
284	SEQ ID NO:289	E333Y	298	SEQ ID NO:303	S239D/A330Y/I332E/K326E
285	SEQ ID NO:290	K334I	299	SEQ ID NO:304	S239D/A330Y/I332E/K326T
286	SEQ ID NO:291	K334T	300	SEQ ID NO:305	S239D/N297D/I332E/A330Y
287	SEQ ID NO:292	K334F	301	SEQ ID NO:306	S239D/N297D/I332E/A330Y /F241S/F243H/V262T/V264T
288	SEQ ID NO:293	T335D	302	SEQ ID NO:307	S239D/N297D/I332E/L235D
289	SEQ ID NO:294	T335R	303	SEQ ID NO:308	S239D/N297D/I332E/K326E

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Please delete Table 62 beginning at page 127 and replace with the following rewritten table:

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Table 62

Variant	SEQ ID NO	Substitution(s)	FcγRIIIa Fold	FcγRIIb Fold	FcγIIIa- fold : FcγIIb- fold
1	SEQ ID NO:9	V264A	0.53		
2	SEQ ID NO:10	V264L	0.56		
3	SEQ ID NO:11	V264I	1.43		
4	SEQ ID NO:12	F241W	0.29		
5	SEQ ID NO:13	F241L	0.26		
6	SEQ ID NO:14	F243W	0.51		
7	SEQ ID NO:15	F243L	0.51		
8	SEQ ID NO:16	F241L/F243L/V262I/V264I	0.09		
9	SEQ ID NO:17	F241W/F243W	0.07		
10	SEQ ID NO:18	F241W/F243W/V262A/V264A	0.04		
11	SEQ ID NO:19	F241L/V262I	0.06		
12	SEQ ID NO:20	F243L/V264I	1.23		

Serial No.: 10/822,231
Filing Date: March 26, 2004

13	<u>SEQ ID NO:21</u>	F243L/V262I/V264W	0.02		
14	<u>SEQ ID NO:22</u>	F241Y/F243Y/V262T/V264T	0.05		
15	<u>SEQ ID NO:23</u>	F241E/F243R/V262E/V264R	0.05		
16	<u>SEQ ID NO:24</u>	F241E/F243Q/V262T/V264E	0.07		
17	<u>SEQ ID NO:25</u>	F241R/F243Q/V262T/V264R	0.02		
18	<u>SEQ ID NO:26</u>	F241E/F243Y/V262T/V264R	0.05		
19	<u>SEQ ID NO:27</u>	L328M	0.21		
20	<u>SEQ ID NO:28</u>	L328E	0.12		
21	<u>SEQ ID NO:29</u>	L328F	0.24		
22	<u>SEQ ID NO:30</u>	I332E	6.72	3.93	1.71
23	<u>SEQ ID NO:31</u>	L328M/I332E	2.60		
24	<u>SEQ ID NO:32</u>	P244H	0.83		
25	<u>SEQ ID NO:33</u>	P245A	0.25		
26	<u>SEQ ID NO:34</u>	P247V	0.53		
27	<u>SEQ ID NO:35</u>	W313F	0.88		
28	<u>SEQ ID NO:36</u>	P244H/P245A/P247V	0.93		
29	<u>SEQ ID NO:37</u>	P247G	0.54		
30	<u>SEQ ID NO:38</u>	V264I/I332E	12.49	1.57*	7.96
31	<u>SEQ ID NO:39</u>	F241E/F243R/V262E/V264R/I332E	0.19		
32	<u>SEQ ID NO:40</u>	F241E/F243Q/V262T/V264E/I332E			
33	<u>SEQ ID NO:41</u>	F241R/F243Q/V262T/V264R/I332E			
34	<u>SEQ ID NO:42</u>	F241E/F243Y/V262T/V264R/I332E	0.10		
35	<u>SEQ ID NO:43</u>	S298A	2.21		
36	<u>SEQ ID NO:44</u>	S298A/I332E	21.73		
37	<u>SEQ ID NO:45</u>	S298A/E333A/K334A	2.56		
41	<u>SEQ ID NO:46</u>	S239E/I332E	5.80	3.49	1.66
42	<u>SEQ ID NO:47</u>	S239Q/I332E	6.60	4.68	1.41
43	<u>SEQ ID NO:48</u>	S239E	10.16		
44	<u>SEQ ID NO:49</u>	D265G	<0.02		
45	<u>SEQ ID NO:50</u>	D265N	<0.02		
46	<u>SEQ ID NO:51</u>	S239E/D265G	<0.02		
47	<u>SEQ ID NO:52</u>	S239E/D265N	0.02		
48	<u>SEQ ID NO:53</u>	S239E/D265Q	0.05		
49	<u>SEQ ID NO:54</u>	Y296E	0.73	1.11	0.66
50	<u>SEQ ID NO:55</u>	Y296Q	0.52	0.43	1.21

Please delete Table 62 (continued) beginning at page 128 and replace with the following rewritten table:

Table 62 (continued)

Variant	<u>SEQ ID NO</u>	Substitution(s)	FcγRIIIa Fold	FcγRIIb Fold	FcγIIIa-fold : FcγIIb-fold
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Serial No.: 10/822,231
Filing Date: March 26, 2004

51	<u>SEQ ID NO:56</u>	S298T	0.94	<0.02	
52	<u>SEQ ID NO:57</u>	S298N	0.41	<0.02	
53	<u>SEQ ID NO:58</u>	T299I	<0.02		
54	<u>SEQ ID NO:59</u>	A327S	0.23	0.39	0.59
55	<u>SEQ ID NO:60</u>	A327N	0.19	1.15	0.17
56	<u>SEQ ID NO:61</u>	S267Q/A327S	0.03		
57	<u>SEQ ID NO:62</u>	S267L/A327S	<0.02		
58	<u>SEQ ID NO:63</u>	A327L	0.05		
59	<u>SEQ ID NO:64</u>	P329F	<0.02		
60	<u>SEQ ID NO:65</u>	A330L	0.73	0.38	1.92
61	<u>SEQ ID NO:66</u>	A330Y	1.64	0.75	2.19
62	<u>SEQ ID NO:67</u>	I332D	17.80	3.34	5.33
63	<u>SEQ ID NO:68</u>	N297S	<0.02		
64	<u>SEQ ID NO:69</u>	N297D	<0.02		
65	<u>SEQ ID NO:70</u>	N297S/I332E	<0.02		
66	<u>SEQ ID NO:71</u>	N297D/I332E	0.08	<0.02	
67	<u>SEQ ID NO:72</u>	N297E/I332E	<0.02		
68	<u>SEQ ID NO:73</u>	D265Y/N297D/I332E	<0.02		
69	<u>SEQ ID NO:74</u>	D265Y/N297D/T299L/I332E	<0.02		
70	<u>SEQ ID NO:75</u>	D265F/N297E/I332E	<0.02		
71	<u>SEQ ID NO:76</u>	L328I/I332E	7.03		
72	<u>SEQ ID NO:77</u>	L328Q/I332E	1.54		
73	<u>SEQ ID NO:78</u>	I332N	0.39		
74	<u>SEQ ID NO:79</u>	I332Q	0.37		
75	<u>SEQ ID NO:80</u>	V264T	2.73		
76	<u>SEQ ID NO:81</u>	V264F	0.16		
77	<u>SEQ ID NO:82</u>	V240I	3.25		
78	<u>SEQ ID NO:83</u>	V263I	0.10		
79	<u>SEQ ID NO:84</u>	V266I	1.86		
80	<u>SEQ ID NO:85</u>	T299A	0.03		
81	<u>SEQ ID NO:86</u>	T299S	0.15		
82	<u>SEQ ID NO:87</u>	T299V	<0.02		
83	<u>SEQ ID NO:88</u>	N325Q	<0.02		
84	<u>SEQ ID NO:89</u>	N325L	<0.02		
85	<u>SEQ ID NO:90</u>	N325I	<0.02		
86	<u>SEQ ID NO:91</u>	S239D	11.64	4.47*	2.60
87	<u>SEQ ID NO:92</u>	S239N	<0.02		
88	<u>SEQ ID NO:93</u>	S239F	0.22	<0.02	
89	<u>SEQ ID NO:94</u>	S239D/I332D	14.10		
90	<u>SEQ ID NO:95</u>	S239D/I332E	56.10	19.71*	2.85
91	<u>SEQ ID NO:96</u>	S239D/I332N	7.19		
92	<u>SEQ ID NO:97</u>	S239D/I332Q	9.28		
93	<u>SEQ ID NO:98</u>	S239E/I332D	9.33		
94	<u>SEQ ID NO:99</u>	S239E/I332N	11.93		
95	<u>SEQ ID NO:100</u>	S239E/I332Q	3.80		
96	<u>SEQ ID NO:101</u>	S239N/I332D	3.08		

Serial No.: 10/822,231
Filing Date: March 26, 2004

97	<u>SEQ ID NO:102</u>	S239N/I332E	14.21		
98	<u>SEQ ID NO:103</u>	S239N/I332N	0.43		

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Please delete Table 62 (continued) beginning at page 129 and replace with the following rewritten table:

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Table 62 (continued)

Variant	<u>SEQ ID NO</u>	Substitution(s)	FcγRIIIa Fold	FcγRIIb Fold	FcγIIIa-fold : FcγIIb- fold
99	<u>SEQ ID NO:104</u>	S239N/I332Q	0.56		
100	<u>SEQ ID NO:105</u>	S239Q/I332D	5.05		
101	<u>SEQ ID NO:106</u>	S239Q/I332N	0.39		
102	<u>SEQ ID NO:107</u>	S239Q/I332Q	0.59		
103	<u>SEQ ID NO:108</u>	K326E	3.85		
104	<u>SEQ ID NO:109</u>	Y296D	0.62		
105	<u>SEQ ID NO:110</u>	Y296N	0.29		
106	<u>SEQ ID NO:111</u>	F241Y/F243Y/V262T/V264T/ N297D/I332E	0.15		
107	<u>SEQ ID NO:112</u>	A330Y/I332E	12.02	4.40	2.73
108	<u>SEQ ID NO:113</u>	V264I/A330Y/I332E	12.00	3.54	3.39
109	<u>SEQ ID NO:114</u>	A330L/I332E	10.34	2.03	5.09
110	<u>SEQ ID NO:115</u>	V264I/A330L/I332E	11.15	1.79	6.23
111	<u>SEQ ID NO:116</u>	L234D	0.21		
112	<u>SEQ ID NO:117</u>	L234E	1.34	2.21	0.61
113	<u>SEQ ID NO:118</u>	L234N	0.56	1.39	0.40
114	<u>SEQ ID NO:119</u>	L234Q	0.37		
115	<u>SEQ ID NO:120</u>	L234T	0.35		
116	<u>SEQ ID NO:121</u>	L234H	0.33		
117	<u>SEQ ID NO:122</u>	L234Y	1.42	1.08	1.31
118	<u>SEQ ID NO:123</u>	L234I	1.55	1.14	1.36
119	<u>SEQ ID NO:124</u>	L234V	0.38		
120	<u>SEQ ID NO:125</u>	L234F	0.30		
121	<u>SEQ ID NO:126</u>	L235D	1.66	3.63	0.46
122	<u>SEQ ID NO:127</u>	L235S	1.25		
123	<u>SEQ ID NO:128</u>	L235N	0.40		
124	<u>SEQ ID NO:129</u>	L235Q	0.51		
125	<u>SEQ ID NO:130</u>	L235T	0.52		
126	<u>SEQ ID NO:131</u>	L235H	0.41		
127	<u>SEQ ID NO:132</u>	L235Y	1.19	10.15	0.12
128	<u>SEQ ID NO:133</u>	L235I	1.10	0.94	1.17
129	<u>SEQ ID NO:134</u>	L235V	0.48		
130	<u>SEQ ID NO:135</u>	L235F	0.73	3.53	0.21
131	<u>SEQ ID NO:136</u>	S239T	1.34		

Serial No.: 10/822,231
Filing Date: March 26, 2004

132	<u>SEQ ID NO:137</u>	S239H	0.20		
133	<u>SEQ ID NO:138</u>	S239Y	0.21		
134	<u>SEQ ID NO:139</u>	V240A	0.70	0.14	5.00
135	<u>SEQ ID NO:140</u>	V240T			
136	<u>SEQ ID NO:141</u>	V240M	2.06	1.38	1.49
137	<u>SEQ ID NO:142</u>	V263A			
138	<u>SEQ ID NO:143</u>	V263T	0.43		
139	<u>SEQ ID NO:144</u>	V263M	0.05		
140	<u>SEQ ID NO:145</u>	V264M	0.26		
141	<u>SEQ ID NO:146</u>	V264Y	1.02	0.27	3.78
142	<u>SEQ ID NO:147</u>	V266A	<0.02		
143	<u>SEQ ID NO:148</u>	V266T	0.45		
144	<u>SEQ ID NO:149</u>	V266M	0.62		
145	<u>SEQ ID NO:150</u>	E269H	<0.02		
146	<u>SEQ ID NO:151</u>	E269Y	0.12		

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Please delete Table 62 (continued) beginning at page 130 and replace with the following rewritten table:

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Table 62 (continued)

Variant	<u>SEQ ID NO</u>	Substitution(s)	FcγRIIIa Fold	FcγRIIb Fold	FcγIIIa-fold : FcγIIb- fold
147	<u>SEQ ID NO:152</u>	E269F	0.16		
148	<u>SEQ ID NO:153</u>	E269R	0.05		
149	<u>SEQ ID NO:154</u>	Y296S	0.12		
150	<u>SEQ ID NO:155</u>	Y296T	<0.02		
151	<u>SEQ ID NO:156</u>	Y296L	0.22		
152	<u>SEQ ID NO:157</u>	Y296I	0.09		
153	<u>SEQ ID NO:158</u>	A298H	0.27		
154	<u>SEQ ID NO:159</u>	T299H	<0.02		
155	<u>SEQ ID NO:160</u>	A330V	0.43		
156	<u>SEQ ID NO:161</u>	A330I	1.71	0.02	85.5
157	<u>SEQ ID NO:162</u>	A330F	0.60		
158	<u>SEQ ID NO:163</u>	A330R	<0.02		
159	<u>SEQ ID NO:164</u>	A330H	0.52		
160	<u>SEQ ID NO:165</u>	N325D	0.41		
161	<u>SEQ ID NO:166</u>	N325E	<0.02		
162	<u>SEQ ID NO:167</u>	N325A	0.11		
163	<u>SEQ ID NO:168</u>	N325T	1.10		
164	<u>SEQ ID NO:169</u>	N325V	0.48		
165	<u>SEQ ID NO:170</u>	N325H	0.73		
166	<u>SEQ ID NO:171</u>	L328D/I332E	1.34		
167	<u>SEQ ID NO:172</u>	L328E/I332E	0.20		

Serial No.: 10/822,231
Filing Date: March 26, 2004

168	<u>SEQ ID NO:173</u>	L328N/I332E	<0.02		
169	<u>SEQ ID NO:174</u>	L328Q/I332E	0.70		
170	<u>SEQ ID NO:175</u>	L328V/I332E	2.06		
171	<u>SEQ ID NO:176</u>	L328T/I332E	1.10		
172	<u>SEQ ID NO:177</u>	L328H/I332E	<0.02		
173	<u>SEQ ID NO:178</u>	L328I/I332E	3.49		
174	<u>SEQ ID NO:179</u>	L328A	0.20		
175	<u>SEQ ID NO:180</u>	I332T	0.72		
176	<u>SEQ ID NO:181</u>	I332H	0.46		
177	<u>SEQ ID NO:182</u>	I332Y	0.76		
178	<u>SEQ ID NO:183</u>	I332A	0.89		
179	<u>SEQ ID NO:184</u>	S239E/V264I/I332E	15.46		
180	<u>SEQ ID NO:185</u>	S239Q/V264I/I332E	2.14		
181	<u>SEQ ID NO:186</u>	S239E/V264I/A330Y/I332E	8.53		
182	<u>SEQ ID NO:187</u>	S239E/V264I/S298A/A330Y/I332E			
183	<u>SEQ ID NO:188</u>	S239D/N297D/I332E	0.28		
184	<u>SEQ ID NO:189</u>	S239E/N297D/I332E	0.06		
185	<u>SEQ ID NO:190</u>	S239D/D265V/N297D/I332E	0.03		
186	<u>SEQ ID NO:191</u>	S239D/D265I/N297D/I332E	0.01		
187	<u>SEQ ID NO:192</u>	S239D/D265L/N297D/I332E	<0.02		
188	<u>SEQ ID NO:193</u>	S239D/D265F/N297D/I332E	<0.02		
189	<u>SEQ ID NO:194</u>	S239D/D265Y/N297D/I332E	0.02		
190	<u>SEQ ID NO:195</u>	S239D/D265H/N297D/I332E	0.04		
191	<u>SEQ ID NO:196</u>	S239D/D265T/N297D/I332E	<0.02		
192	<u>SEQ ID NO:197</u>	V264E/N297D/I332E	0.05		
193	<u>SEQ ID NO:198</u>	Y296D/N297D/I332E			
194	<u>SEQ ID NO:199</u>	Y296E/N297D/I332E	<0.02		

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Please delete Table 62 (continued) beginning at page 131 and replace with the following rewritten table:

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Table 62 (continued)

Variant	<u>SEQ ID NO</u>	Substitution(s)	FcγRIIIa Fold	FcγRIIb Fold	FcγIIIa-fold : FcγIIb-fold
195	<u>SEQ ID NO:200</u>	Y296N/N297D/I332E	0.04		
196	<u>SEQ ID NO:201</u>	Y296Q/N297D/I332E	<0.02		
197	<u>SEQ ID NO:202</u>	Y296H/N297D/I332E	<0.02		
198	<u>SEQ ID NO:203</u>	Y296T/N297D/I332E	<0.02		
199	<u>SEQ ID NO:204</u>	N297D/T299V/I332E	<0.02		
200	<u>SEQ ID NO:205</u>	N297D/T299I/I332E	<0.02		
201	<u>SEQ ID NO:206</u>	N297D/T299L/I332E	<0.02		
202	<u>SEQ ID NO:207</u>	N297D/T299F/I332E	<0.02		
203	<u>SEQ ID NO:208</u>	N297D/T299H/I332E	<0.02		
204	<u>SEQ ID NO:209</u>	N297D/T299E/I332E	<0.02		

Serial No.: 10/822,231
Filing Date: March 26, 2004

205	<u>SEQ ID NO:210</u>	N297D/A330Y/I332E	0.43		
206	<u>SEQ ID NO:211</u>	N297D/S298A/A330Y/I332E	0.16		
207	<u>SEQ ID NO:212</u>	S239D/A330Y/I332E	129.58		
208	<u>SEQ ID NO:213</u>	S239N/A330Y/I332E	14.22		
209	<u>SEQ ID NO:214</u>	S239D/A330L/I332E	138.63	7.50	18.48
210	<u>SEQ ID NO:215</u>	S239N/A330L/I332E	12.95		
211	<u>SEQ ID NO:216</u>	V264I/S298A/I332E	16.50		
212	<u>SEQ ID NO:217</u>	S239D/S298A/I332E	295.16	6.16	47.92
213	<u>SEQ ID NO:218</u>	S239N/S298A/I332E	32.14	5.15	6.24
214	<u>SEQ ID NO:219</u>	S239D/V264I/I332E	36.58	14.39	2.54
215	<u>SEQ ID NO:220</u>	S239D/V264I/S298A/I332E			
216	<u>SEQ ID NO:221</u>	S239D/V264I/A330L/I332E			
217	<u>SEQ ID NO:222</u>	L328N	0.59		
218	<u>SEQ ID NO:223</u>	L328H	<0.02		
219	<u>SEQ ID NO:224</u>	S239D/I332E/A330I	59.1		
220	<u>SEQ ID NO:225</u>	N297D/I332E/S239D/A330L			
221	<u>SEQ ID NO:226</u>	P230A	1.09		
222	<u>SEQ ID NO:227</u>	E233D	0.85		
223	<u>SEQ ID NO:228</u>	P230A/E233D	0.92		
224	<u>SEQ ID NO:229</u>	P230A/E233D/I332E	1.87		
225	<u>SEQ ID NO:230</u>	S267T			
226	<u>SEQ ID NO:231</u>	S267H			
227	<u>SEQ ID NO:232</u>	S267D			
228	<u>SEQ ID NO:233</u>	S267N			
229	<u>SEQ ID NO:234</u>	E269T	<0.02		
230	<u>SEQ ID NO:235</u>	E269L	<0.02		
231	<u>SEQ ID NO:236</u>	E269N	<0.02		
232	<u>SEQ ID NO:237</u>	D270Q	<0.02		
233	<u>SEQ ID NO:238</u>	D270T	<0.02		
234	<u>SEQ ID NO:239</u>	D270H	<0.02		
235	<u>SEQ ID NO:240</u>	E272S			
236	<u>SEQ ID NO:241</u>	E272K			
237	<u>SEQ ID NO:242</u>	E272I			
238	<u>SEQ ID NO:243</u>	E272Y	8.70		
239	<u>SEQ ID NO:244</u>	V273I	0.79		
240	<u>SEQ ID NO:245</u>	K274T	1.41		
241	<u>SEQ ID NO:246</u>	K274E	6.11		
242	<u>SEQ ID NO:247</u>	K274R	1.41		
243	<u>SEQ ID NO:248</u>	K274L	1.09		
244	<u>SEQ ID NO:249</u>	K274Y	1.06		
245	<u>SEQ ID NO:250</u>	F275W	1.11		

Please delete Table 62 (continued) beginning at page 133 and replace with the following rewritten table:

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Table 62 (continued)

Variant	<u>SEQ ID NO</u>	Substitution(s)	FcγRIIIa Fold	FcγRIIb Fold	FcγIIIa-fold : FcγIIb- fold
246	<u>SEQ ID NO:251</u>	N276S	0.41		
247	<u>SEQ ID NO:252</u>	N276E	0.87		
248	<u>SEQ ID NO:253</u>	N276R	0.66		
249	<u>SEQ ID NO:254</u>	N276L	1.07		
250	<u>SEQ ID NO:255</u>	N276Y	0.56		
251	<u>SEQ ID NO:256</u>	Y278T	1.87		
252	<u>SEQ ID NO:257</u>	Y278E	0.90		
253	<u>SEQ ID NO:258</u>	Y278K			
254	<u>SEQ ID NO:259</u>	Y278W	0.41		
255	<u>SEQ ID NO:260</u>	E283R	0.67		
256	<u>SEQ ID NO:261</u>	V302I	1.01		
257	<u>SEQ ID NO:262</u>	E318R	1.06		
258	<u>SEQ ID NO:263</u>	K320T			
259	<u>SEQ ID NO:264</u>	K320D			
260	<u>SEQ ID NO:265</u>	K320I			
261	<u>SEQ ID NO:266</u>	K322T			
262	<u>SEQ ID NO:267</u>	K322H			
263	<u>SEQ ID NO:268</u>	V323I	0.83		
264	<u>SEQ ID NO:269</u>	S324T			
265	<u>SEQ ID NO:270</u>	S324D	1.07		
266	<u>SEQ ID NO:271</u>	S324R	0.71		
267	<u>SEQ ID NO:272</u>	S324I	1.15		
268	<u>SEQ ID NO:273</u>	S324V	1.17		
269	<u>SEQ ID NO:274</u>	S324L	<0.02		
270	<u>SEQ ID NO:275</u>	S324Y	0.98		
271	<u>SEQ ID NO:276</u>	K326L			
272	<u>SEQ ID NO:277</u>	K326I	1.43		
273	<u>SEQ ID NO:278</u>	K326T	1.88		
274	<u>SEQ ID NO:279</u>	A327D	<0.02		
275	<u>SEQ ID NO:280</u>	A327T	<0.02		
276	<u>SEQ ID NO:281</u>	A330S			
277	<u>SEQ ID NO:282</u>	A330W			
278	<u>SEQ ID NO:283</u>	A330M			
279	<u>SEQ ID NO:284</u>	P331V			
280	<u>SEQ ID NO:285</u>	P331H			
281	<u>SEQ ID NO:286</u>	E333T	0.78		
282	<u>SEQ ID NO:287</u>	E333H	0.75		
283	<u>SEQ ID NO:288</u>	E333I			
284	<u>SEQ ID NO:289</u>	E333Y			

285	<u>SEQ ID NO:290</u>	K334I			
286	<u>SEQ ID NO:291</u>	K334T			
287	<u>SEQ ID NO:292</u>	K334F			
288	<u>SEQ ID NO:293</u>	T335D	2.79		
289	<u>SEQ ID NO:294</u>	T335R	2.58		
290	<u>SEQ ID NO:295</u>	T335Y	1.56		
291	<u>SEQ ID NO:296</u>	L234I/L235D	0.07		
292	<u>SEQ ID NO:297</u>	V240I/V266I	1.72		
293	<u>SEQ ID NO:298</u>	S239D/A330Y/I332E/L234I	22.39		
294	<u>SEQ ID NO:299</u>	S239D/A330Y/I332E/L235D	7.04		
295	<u>SEQ ID NO:300</u>	S239D/A330Y/I332E/V240I	27.97		
296	<u>SEQ ID NO:301</u>	S239D/A330Y/I332E/V264T	17.72		
297	<u>SEQ ID NO:302</u>	S239D/A330Y/I332E/V266I			
298	<u>SEQ ID NO:303</u>	S239D/A330Y/I332E/K326E	64.14		
299	<u>SEQ ID NO:304</u>	S239D/A330Y/I332E/K326T	59.03		
300	<u>SEQ ID NO:305</u>	S239D/N297D/I332E/A330Y	<0.02		
301	<u>SEQ ID NO:306</u>	S239D/N297D/I332E/A330Y/ F241S/F243H/V262T/V264T	<0.02		
302	<u>SEQ ID NO:307</u>	S239D/N297D/I332E/L235D			
303	<u>SEQ ID NO:308</u>	S239D/N297D/I332E/K326E			

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Please delete the paragraph beginning at page 134, paragraph [211] and replace with the following rewritten paragraph:

--[211] Example 3: Selectively enhanced binding to FcγRs

A number of promising Fc variants with optimized properties were obtained from the FcγRIIIa and FcγRIIb screen. Table 62 provides Fc variants that bind more tightly to FcγRIIIa, and thus are candidates for improving the effector function of antibodies and Fc fusions. These include a number of variants that comprise substitutions at 239, 264, 272, 274, 330, and 332. Figures 13a and 13b show AlphaScreen™ binding data for some of these Fc variants. The majority of these Fc variants provide substantially greater FcγRIIIa binding enhancements over S298A/E333A/K334A (SEQ ID NO:45).--

Please delete the paragraph and table beginning at page 136, paragraph [218] and replace with the following rewritten paragraph:

--[214] Some of the most promising Fc variants of the present invention for enhancing effector function have both substantial increases in affinity for FcγRIIIa and favorable FcγRIIIa-fold:FcγRIIb-fold ratios. These include, for example, S239D/I332E (SEQ ID NO:95) (FcγRIIIa-fold = 56, FcγRIIIa-fold:FcγRIIb-fold = 3), S239D/A330Y/I332E (SEQ ID NO:212) (FcγRIIIa-fold = 130), S239D/A330L/I332E (SEQ ID NO:214) (FcγRIIIa-fold = 139, FcγRIIIa-fold:FcγRIIb-fold = 18), and S239D/S298A/I332E (SEQ ID

NO:217) (FcγRIIIa-fold = 295, FcγRIIIa-fold:FcγRIIb-fold = 48). Figure 17 shows AlphaScreen™ binding data for these and other Fc variants to human V158 FcγRIIIa.--

Please delete the paragraph and table beginning at page 135, paragraph [218] and replace with the following rewritten paragraph:

--[218] Example 5: Aglycosylated Fc variants

As discussed, one goal of the current experiments was to obtain optimized aglycosylated Fc variants. Several Fc variants provide significant progress towards this goal. Because it is the site of glycosylation, substitution at N297 results in an aglycosylated Fc. Whereas all other Fc variants that comprise a substitution at N297 completely ablate FcγR binding, N297D/I332E (SEQ ID NO:71) has significant binding affinity for FcγRIIIa, shown in Table 62 and illustrated in Figure 20. The exact reason for this result is uncertain in the absence of a high-resolution structure for this variant, although the computational screening predictions suggest that it is potentially due to a combination of new favorable Fc/FcγR interactions and favorable electrostatic properties. Indeed other electrostatic substitutions are envisioned for further optimization of aglycosylated Fc. Table 62 shows that other aglycosylated Fc variants such as S239D/N297D/I332E (SEQ ID NO:188) and N297D/A330Y/I332E (SEQ ID NO:210) provide binding enhancements that bring affinity for FcγRIIIa within 0.28- and 0.43-fold respectively of glycosylated WT alemtuzumab. Combinations of these variants with other Fc variants that enhance FcγR binding are contemplated, with the goal of obtaining aglycosylated Fc variants that bind one or more FcγRs with affinity that is approximately the same as or even better than glycosylated parent Fc. An additional set of promising Fc variants provide stability and solubility enhancements in the absence of carbohydrate. Fc variants that comprise substitutions at positions 241, 243, 262, and 264, positions that do not mediate FcγR binding but do determine the interface between the carbohydrate and Fc, ablate FcγR binding, presumably because they perturb the conformation of the carbohydrate. In deglycosylated form, however, Fc variants F241E/F243R/V262E/V264R (SEQ ID NO:23), F241E/F243Q/V262T/V264E (SEQ ID NO:24), F241R/F243Q/V262T/V264R (SEQ ID NO:25), and F241E/F243Y/V262T/V264R (SEQ ID NO:26) show stronger binding to FcγRIIIa than in glycosylated form, as shown by the AlphaScreen™ data in Figure 21. This result indicates that these are key positions for optimization of the structure, stability, solubility, and function of aglycosylated Fc. Together these results suggests that protein engineering can be used to restore the favorable functional and solution properties of antibodies and Fc fusions in the absence of carbohydrate, and pave the way for aglycosylated antibodies and Fc fusions with favorable solution properties and full functionality that comprise substitutions at these and other Fc positions.--

Please delete Table 63 beginning at page 137 and replace with the following rewritten table:

Table 63

	SPR V158 FcγRIIIa		SPR F158 FcγRIIIa		AlphaScreen™ V158 FcγRIIIa		AlphaScreen™ F158 FcγRIIIa	
	Kd (nM)	Fold	Kd (nM)	Fold	IC50 (nM)	Fold	IC50 (nM)	Fold
WT (SEQ ID NO:2)	68		730		6.4		17.2	
V264I (SEQ ID NO:11)	64	1.1	550	1.3	4.5	1.4	11.5	1.5
I332E (SEQ ID NO:30)	31	2.2	72	10.1	1.0	6.4	2.5	6.9
V264I/I332E (SEQ ID NO:38)	17	4.0	52	14.0	0.5	12.8	1.1	15.6
S298A (SEQ ID NO:43)	52	1.3	285	2.6	2.9	2.2	12.0	1.4
S298A/E333A/ K334A (SEQ ID NO:45)	39	1.7	156	4.7	2.5	2.6	7.5	2.3

Please delete the paragraph beginning at page 137, paragraph [221] and replace with the following rewritten paragraph:

--[221] The SPR data corroborate the improvements to FcγRIIIa affinity observed by AlphaScreen™ assay. Table 63 further indicates the superiority of V264I/I332E (SEQ ID NO:38) and I332E (SEQ ID NO:30) over S298A (SEQ ID NO:43) and S298A/E333A/K334A (SEQ ID NO:45); whereas S298A/E333A/K334A (SEQ ID NO:45) improves Fc binding to V158 and F158 FcγRIIIa by 1.7-fold and 4.7-fold respectively, I332E (SEQ ID NO:30) shows binding enhancements of 2.2-fold and 10.1-fold respectively, and V264I/I332E (SEQ ID NO:38) shows binding enhancements of 4.0-fold and 14-fold respectively. Also worth noting is that the affinity of V264I/I332E (SEQ ID NO:38) for F158 FcγRIIIa (52 nM) is better than that of WT for the V158 allotype (68 nM), suggesting that this Fc variant, as well as those with even greater improvements in binding, may enable the clinical efficacy of antibodies for the low responsive patient population to achieve that currently possible for high responders. The correlation between the SPR and AlphaScreen™ binding measurements are shown in Figures 23a – 23d. Figures 23a and 23b show the Kd - IC50 correlations for binding to V158 FcγRIIIa and F158 FcγRIIIa respectively, and Figures 23c and 23d show the fold-improvement correlations for binding to V158 FcγRIIIa and F158 FcγRIIIa respectively. The good fits of these data to straight lines ($r^2 = 0.9$, $r^2 = 0.84$, $r^2 = 0.98$, and $r^2 =$

0.90) support the accuracy the AlphaScreen™ measurements, and validate its use for determining the relative FcγR binding affinities of Fc variants.--

Please delete the paragraph beginning at page 138, paragraph [222] and replace with the following rewritten paragraph:

--[222] SPR data were also acquired for binding of select trastuzumab Fc variants to human V158 FcγRIIIa, F158 FcγRIIIa, and FcγRIIb. These data are shown in Table 64. The Fc variants tested show substantial binding enhancements to the activating receptor FcγRIIIa, with over 100-fold tighter binding observed for interaction of S239D/I332E/S298A (SEQ ID NO:217) with F158 FcγRIIIa. Furthermore, for the best FcγRIIIa binders, F158 FcγRIIIa/FcγRIIb ratios of 3 – 4 are observed.--

Please delete Table 64 beginning at page 138 and replace with the following rewritten table:

--
Table 64

	SPR V158 FcγRIIIa		SPR F158 FcγRIIIa		SPR FcγRIIb	
	Kd (nM)	Fold	Kd (nM)	Fold	IC50 (nM)	Fold
WT (SEQ ID NO:2)	363.5		503		769	
V264I/I332E (SEQ ID NO:38)	76.9	4.7	252	2.0	756	1.0
V264I/I332E/A330L (SEQ ID NO:115)	113.0	3.2	88	5.7	353	2.2
S239D/I332E/A330L (SEQ ID NO:214)	8.2	44.3	8.9	56.5	46	16.7
S239D/I332E/S298A (SEQ ID NO:217)	8.7	41.8	4.9	102.7	32	24.0
S239D/I332E/V264I/A330L (SEQ ID NO:221)	12.7	28.6	6.3	79.8	35	22.0

--

Please delete the paragraph beginning at page 138, paragraph [222] and replace with the following rewritten paragraph:

--[224] ADCC assays were run on Fc variant and WT alemtuzumab using DoHH-2 lymphoma target cells. Figure 24a is a bar graph showing the ADCC of these proteins at 10 ng/ml antibody. Results show that alemtuzumab Fc variants I332E (SEQ ID NO:30), V264I (SEQ ID NO:11), and I332E/V264I (SEQ ID NO:38) have substantially enhanced ADCC compared to WT alemtuzumab, with the relative ADCC enhancements proportional to their binding improvements to FcγRIIIa as indicated by AlphaScreen™ assay and SPR. The dose dependence of ADCC on antibody concentration is shown in Figure 24b. The binding data were normalized to the minimum and maximum fluorescence signal for each particular curve, provided by the baselines at low and high antibody concentrations respectively. The data were fit

to a sigmoidal dose-response model using nonlinear regression, represented by the curve in the figure. The fits enable determination of the effective concentration 50% (EC50) (i.e. the concentration required for 50% effectiveness), which provides the relative enhancements to ADCC for each Fc variant. The EC50s for these binding data are analogous to the IC50s obtained from the AlphaScreen™ competition data, and derivation of these values is thus analogous to that described in Example 2 and Figure 11. In Figure 24b, the log(EC50)s, obtained from the fits to the data, for WT (SEQ ID NO:2), V264I/I332E (SEQ ID NO:38), and S239D/I332E (SEQ ID NO:95) alemtuzumab are 0.99, 0.60, and 0.49 respectively, and therefore their respective EC50s are 9.9, 4.0, and 3.0. Thus V264I/I332E (SEQ ID NO:38) and S239E/I332E (SEQ ID NO:95) provide a 2.5-fold and 3.3-fold enhancement respectively in ADCC over WT alemtuzumab using PBMCs expressing heterozygous V158/F158 FcγRIIIa. These data are summarized in Table 65 below.--

Please delete Table 65 beginning at page 139 and replace with the following rewritten table:

--
Table 65

	log(EC50)	EC50 (ng/ml)	Fold Improvement Over WT
WT (SEQ ID NO:2)	0.99	9.9	
V264I/I332E (SEQ ID NO:38)	0.60	4.0	2.5
S239D/I332E (SEQ ID NO:95)	0.49	3.0	3.3

--

Please delete the paragraph beginning at page 139, paragraph [225] and replace with the following rewritten paragraph:

--[225] In order to determine whether these ADCC enhancements are broadly applicable to antibodies, select Fc variants were evaluated in the context of trastuzumab and rituximab. ADCC assays were run on Fc variant and WT trastuzumab using two breast carcinoma target cell lines BT474 and Sk-Br-3. Figure 25a shows a bar graph illustrating ADCC at 1 ng/ml antibody. Results indicate that V264I (SEQ ID NO:11) and V264I/I332E (SEQ ID NO:38) trastuzumab provide substantially enhanced ADCC compared to WT trastuzumab, with the relative ADCC enhancements proportional to their binding improvements to FcγRIIIa as indicated by AlphaScreen™ assay and SPR. Figures 25b and 25c show the dose dependence of ADCC on antibody concentration for select Fc variants. The EC50s obtained from the fits of these data and the relative fold-improvements in ADCC are provided in Table 66 below. Significant ADCC improvements are observed for I332E (SEQ ID NO:30) trastuzumab when combined with A330L (SEQ ID NO:65) and A330Y (SEQ ID NO:66). Furthermore, S239D/A330L/I332E (SEQ ID NO:214) provides

a substantial ADCC enhancement, greater than 300-fold for PBMCs expressing homozygous F158/F158 FcγRIIIa, relative to WT trastuzumab and S298A/E333A/K334A(SEQ ID NO:45), consistent with the FcγR binding data observed by the AlphaScreen™ assay and SPR.--

Please delete Table 66 beginning at page 140 and replace with the following rewritten table:

Table 66

	log(EC50)	EC50 (ng/ml)	Fold Improvement Over WT
Figure 25b			
WT (SEQ ID NO:2)	1.1	11.5	
I332E (SEQ ID NO:30)	0.34	2.2	5.2
A330Y/I332E (SEQ ID NO:112)	-0.04	0.9	12.8
A330L/I332E (SEQ ID NO:114)	0.04	1.1	10.5
Figure 25d			
WT (SEQ ID NO:2)	-0.15	0.71	
S298A/E333A/K334A (SEQ ID NO:45)	-0.72	0.20	3.6
S239D/A330L/I332E (SEQ ID NO:214)	-2.65	0.0022	323

Please delete the paragraph beginning at page 140, paragraph [226] and replace with the following rewritten paragraph:

--[226] ADCC assays were run on V264I/I332E (SEQ ID NO:38), WT (SEQ ID NO:2), and S298A/ΔE333A/K334A (SEQ ID NO:45) rituximab using WIL2-S lymphoma target cells. Figure 26a presents a bar graph showing the ADCC of these proteins at 1 ng/ml antibody. Results indicate that V264I/I332E (SEQ ID NO:38) rituximab provides substantially enhanced ADCC relative to WT rituximab, as well as superior ADCC to S298A/ΔE333A/K334A (SEQ ID NO:45), consistent with the FcγRIIIa binding improvements observed by AlphaScreen™ assay and SPR. Figures 26b and 26c show the dose dependence of ADCC on antibody concentration for select Fc variants. The EC50s obtained from the fits of these data and the relative fold-improvements in ADCC are provided in Table 67 below. As can be seen S239D/I332E/A330L (SEQ ID NO:214) rituximab provides greater than 900-fold enhancement in EC50 over WT for PBMCs expressing homozygous F158/F158 FcγRIIIa. The differences in ADCC enhancements observed for alemtuzumab, trastuzumab, and rituximab are likely due to the use of different PBMCs, different antibodies, and different target cell lines.--

Please delete Table 67 beginning at page 140 and replace with the following rewritten table:

Table 67

	log(EC50)	EC50 (ng/ml)	Fold Improvement Over WT
Figure 26b			
WT (SEQ ID NO:2)	0.23	1.7	
S298A/E333A/K334A (SEQ ID NO:45)	-0.44	0.37	4.6
V264I/I332E (SEQ ID NO:38)	-0.83	0.15	11.3
Figure 26c			
WT (SEQ ID NO:2)	0.77	5.9	
S239D/I332E/A330L (SEQ ID NO:214)	-2.20	0.0063	937

Please delete the paragraph beginning at page 141, paragraph [228] and replace with the following rewritten paragraph:

--[228] A critical parameter governing the clinical efficacy of anti-cancer antibodies is the expression level of target antigen on the surface of tumor cells. Thus a major clinical advantage of Fc variants that enhance ADCC may be that it enables the targeting of tumors that express lower levels of antigen. In To test this hypothesis, WT and Fc variant trastuzumab antibodies were tested for their ability to mediate ADCC against different cell lines expressing varying levels of the Her2/neu target antigen. ADCC assays were run with various cell lines expressing amplified to low levels of Her2/neu receptor, including Sk-Br-3 (1×10^6 copies), SkOV3 ($\sim 1 \times 10^5$), OVCAR3 ($\sim 1 \times 10^4$), and MCF-7 ($\sim 3 \times 10^3$ copies), using the DELFIA EuTDA Cytotoxicity kit (PerkinElmer, Boston, MA). Target cells were loaded with BATDA in batch for 25 minutes, washed multiple times with medium and seeded at 10,000 cells per well in 96-well plates. Target cells were opsonized for 15 minutes with various antibodies and concentrations (final conc. ranging from 100 ng/ml to .0316 ng/ml in $\frac{1}{2}$ log steps, including no treatment control). Human PBMCs, isolated from buffy-coat and allotyped as homozygous F158/F158 Fc γ RIIIa were then added to opsonized cells at 25-fold excess and co-cultured at 37°C for 4 hrs. Thereafter, plates were centrifuged, supernatants were removed and treated with Eu3+ solution, and relative fluorescence units (correlating to the level of cell lysis) were measured using a Packard Fusion™ α -FP HT reader (PerkinElmer, Boston, MA). The experiment was carried out in triplicates. Figure 28 shows the ADCC data comparing WT and Fc variant trastuzumab against the four different Her2/neu⁺ cell lines. The S239D/I332E (SEQ ID NO:95) and S239D/I332E/A330L (SEQ ID NO:214) variants provide substantial ADCC enhancements over WT

trastuzumab at high, moderate, and low expression levels of target antigen. This result suggests that the Fc variants of the present invention may broaden the therapeutic window of anti-cancer antibodies.--

Please delete the paragraph beginning at page 142, paragraph [230] and replace with the following rewritten paragraph:

--[230] Example 8. ADCP of Fc Variants

Another important FcγR-mediated effector function is ADCP. Phagocytosis of target cancer cells may not only lead to the immediate destruction of target cells, but because phagocytosis is a potential mechanism for antigen uptake and processing by antigen presenting cells, enhanced ADCP may also improve the capacity of the antibody or Fc fusion to elicit an adaptive immune response. The ability of the Fc variants of the present invention to mediate ADCP was therefore investigated. Monocytes were isolated from heterozygous V158/F158 FcγRIIIa PBMCs using a Percoll gradient. After one week in culture in the presence of 0.1 ng/ml, differentiated macrophages were detached with EDTA/PBS- and labeled with the lipophilic fluorophore, PKH26, according to the manufacturer's protocol (Sigma, St Louis, Mo). Sk-Br-3 target cells were labeled with PKH67 (Sigma, St Louis, Mo), seeded in a 96-well plate at 20,000 cells per well, and treated with designated final concentrations of WT or Fc variant trastuzumab. PKH26-labeled macrophages were then added to the opsonized, labeled Sk-Br-3 cells at 20,000 cells per well and the cells were co-cultured for 18 hrs before processing cells for analysis of dual label flow cytometry. Percent phagocytosis was determined as the number of cells co-labeled with PKH76 and PKH26 (macrophage + Sk-Br-3) over the total number of Sk-Br-3 in the population (phagocytosed + non-phagocytosed) after 10,000 counts. Figure 30 shows data comparing WT and Fc variant trastuzumab at various antibody concentrations. The results indicate that the S239D/I332E/A330L (SEQ ID NO:214) variant provides a significant enhancement in ADCP over WT trastuzumab.--

Please delete the paragraph beginning at page 142, paragraph [231] and replace with the following rewritten paragraph:

--[231] Example 9. Complement binding and activation by Fc variants

Complement protein C1q binds to a site on Fc that is proximal to the FcγR binding site, and therefore it was prudent to determine whether the Fc variants have maintained their capacity to recruit and activate complement. The AlphaScreen™ assay was used to measure binding of select Fc variants to the complement protein C1q. The assay was carried out with biotinylated WT alemtuzumab antibody attached to streptavidin donor beads as described in Example 2, and using C1q coupled directly to acceptor beads. Binding data of V264I (SEQ ID NO:11), I332E (SEQ ID NO:30), S239E (SEQ ID

NO:48), and V264I/I332E (SEQ ID NO:38) rituximab shown in Figure 31a indicate that C1q binding is uncompromised. Cell-based CDC assays were also performed on select Fc variants to investigate whether Fc variants maintain the capacity to activate complement. Alamar Blue was used to monitor lysis of Fc variant and WT rituximab-opsonized WIL2-S lymphoma cells by human serum complement (Quidel, San Diego, CA). The data in Figure 31b show that CDC is uncompromised for the Fc variants S239E (SEQ ID NO:48), V264I (SEQ ID NO:11), and V264I/I332E (SEQ ID NO:38) rituximab. In contrast, Figure 31c shows that CDC of the Fc variant S239D/I332E/A330L (SEQ ID NO:214) is completely ablated, whereas the S239D/I332E variant (SEQ ID NO:95) mediates CDC that is comparable to WT rituximab. These results indicate that protein engineering can be used to distinguish between different effector functions. Such control will not only enable the generation of antibodies and Fc fusions with properties tailored for a desired clinical outcome, but also provide a unique set of reagents with which to experimentally investigate effector function biology.--

Please delete the paragraph beginning at page 143, paragraph [233] and replace with the following rewritten paragraph:

--[233] Example 11. Capacity of Fc variants to bind mouse FcγRs

Optimization of Fc to nonhuman FcγRs may be useful for experimentally testing Fc variants in animal models. For example, when tested in mice (for example nude mice, SCID mice, xenograft mice, and/or transgenic mice), antibodies and Fc fusions that comprise Fc variants that are optimized for one or more mouse FcγRs may provide valuable information with regard to clinical efficacy, mechanism of action, and the like. In order to evaluate whether the Fc variants of the present invention may be useful in such experiments, affinity of select Fc variants for mouse FcγRIII was measured using the AlphaScreen™ assay. The AlphaScreen™ assay was carried out using biotinylated WT alemtuzumab attached to streptavidin donor beads as described in Example 2, and GST-tagged mouse FcγRIII bound to glutathione chelate acceptor beads, expressed and purified as described in Example 2. These binding data are shown in Figures 34a and 34b in the context of alemtuzumab and trastuzumab respectively. Results show that some Fc variants that enhance binding to human FcγRIIIa also enhance binding to mouse FcγRIII. The enhancement of mouse effector function by the Fc variants was investigated by performing the aforementioned cell-based ADCC assays using mouse rather than human PBMC's. Figure 35 shows that the S239D/I332E/A330L (SEQ ID NO:214) trastuzumab variant provides substantial ADCC enhancement over WT in the presence of mouse immune cells. This result indicates that the Fc variants of the present invention, or other Fc variants that are optimized for nonhuman FcγRs, may find use in experiments that use animal models.--

Please delete the paragraph beginning at page 144, paragraph [235] and replace with the following rewritten paragraph:

--[235] Example 13. Enhancement of Fc variants in Fucose Minus Strain.

Combinations of the Fc variants of the present invention with other Fc modifications are contemplated with the goal of generating novel antibodies or Fc fusions with optimized properties. It may be beneficial to combine the Fc variants of the present invention with other Fc modifications, including modifications that alter effector function or interaction with one or more Fc ligands. Such combination may provide additive, synergistic, or novel properties in antibodies or Fc fusions. For example, a number of methods exist for engineering different glycoforms of Fc that alter effector function. Engineered glycoforms may be generated by a variety of methods known in the art, many of these techniques are based on controlling the level of fucosylated and/or bisecting oligosaccharides that are covalently attached to the Fc region. One method for engineering Fc glycoforms is to express the Fc polypeptide in a cell line that generates altered glycoforms, for example Lec-13 CHO cells. In order to investigate the properties of Fc variants combined with engineered glycoforms, WT and V209 (S239D/I332E/A330L(SEQ ID NO:214)) trastuzumab were expressed in Lec-13 CHO cells and purified as described above. Figure 37a shows AlphaScreen™ binding data comparing the binding to human V158 FcγRIIIa by WT and V209 trastuzumab expressed in 293T, CHO, and Lec-13 cells. The results show that there is substantial synergy between the engineered glycoforms produced by this cell line and the Fc variants of the present invention. The cell-based ADCC assay, shown in Figure 37b, supports this result. Together these data indicate that other Fc modifications, particularly engineered glycoforms, may be combined with the Fc variants of the present invention to generate antibodies and Fc fusions with optimized effector functions.--

Please delete the paragraph beginning at page 145, paragraph [236] and replace with the following rewritten paragraph:

--[236] Example 14. Therapeutic application of Fc variants

A number of Fc variants described in the present invention have significant potential for improving the therapeutic efficacy of anticancer antibodies. For illustration purposes, a number of Fc variants of the present invention have been incorporated into the sequence of the antibody rituximab. The WT rituximab light chain (SEQ ID NO:3) and heavy chain (SEQ ID NO:4), described in US 5,736,137, are provided in Figures 38a and 38b. The improved anti-CD20 antibody sequences (SEQ ID NO:5) are provided in Figure 38c. The improved anti-CD20 antibody sequences comprise at least non-WT amino acid selected from the group consisting of X₁, X₂, X₃, X₄, X₅, X₆, X₇, and X₈. These improved anti-CD20 antibody sequences may also comprise a substitution Z₁ and/or Z₂. The use of rituximab here is solely an example,

Serial No.: 10/822,231
 Filing Date: March 26, 2004

and is not meant to constrain application of the Fc variants to this antibody or any other particular antibody or Fc fusion.--

Please delete Table 68 beginning at page 146 and replace with the following rewritten table:

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Table 68

Variant	SEQ ID NO	Substitution(s)	FcγRI	FcγRIIa	FcγRIIb	FcγRIIc	FcγRIIIa	FcRn	C1q
111	SEQ ID NO:116	L234D	0.54	1.23	2.91	2.99	2.33	1.60	1.69
112	SEQ ID NO:117	L234E	0.51	0.71	1.65	1.35	2.05	0.15	1.05
113	SEQ ID NO:118	L234N	0.11	0.07	0.90	1.11	0.20	1.64	1.02
114	SEQ ID NO:119	L234Q	0.22	1.51	2.25	2.18	0.11	3.73	0.48
115	SEQ ID NO:120	L234T	0.18	0.95	1.19	2.00	0.25	0.99	1.73
116	SEQ ID NO:121	L234H	0.07	1.75	3.24	1.32	0.09	1.01	1.04
117	SEQ ID NO:122	L234Y	0.36	0.99	1.06	1.32	0.51	0.73	1.15
118	SEQ ID NO:123	L234I	0.48	1.12	1.38	0.60	0.76	1.30	1.97
119	SEQ ID NO:124	L234V	0.86	1.31	3.23	0.93	1.33	1.33	1.39
120	SEQ ID NO:125	L234F	0.13	0.09	1.20	0.35	0.25	1.02	1.94
121	SEQ ID NO:126	L235D	0.04	0.90	1.51	0.71	1.33	0.77	1.26
122	SEQ ID NO:127	L235S	0.12	0.74	1.61	0.64	0.35	0.99	1.04
123	SEQ ID NO:128	L235N	0.03	0.77	1.56	0.76	0.34	1.10	1.46
124	SEQ ID NO:129	L235Q	0.06	0.82	2.33	0.82	0.39	0.39	1.24
125	SEQ ID NO:130	L235T	0.10	0.63	1.39	0.72	1.40	0.93	0.92
126	SEQ ID NO:131	L235H	0.05	1.27	3.36	1.72	0.14	0.33	1.19
127	SEQ ID NO:132	L235Y	0.09	0.79	2.43	0.61	1.09	0.53	1.50
128	SEQ ID NO:133	L235I	0.20	0.24	1.91	0.22	1.16	1.24	0.63
129	SEQ ID NO:134	L235V	0.22	3.30	3.69	2.59	0.91	2.70	1.04
130	SEQ ID NO:135	L235F	0.09	13.07	1.73	1.31	0.79	0.92	1.26

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Please delete Table 69 beginning at page 147 and replace with the following rewritten table:

--Table 69

Variant	SEQ ID NO	Substitution(s)	FcγRI	FcγRIIa	FcγRIIb	FcγRIIc	FcγRIIIa	FcRn	C1q
107	SEQ ID NO:112	A330Y/I332E	3.14	5.40	2.90	3.84	19.33	2.35	1.15
109	SEQ ID NO:114	A330L/I332E	6.44	1.53	1.16	1.53	21.23	5.36	1.03
167	SEQ ID NO:172	L328E/I332E	0.91	3.50	5.54	10.21	3.35	0.31	
171	SEQ ID NO:176	L328T/I332E	1.42	3.07	10.23	22.69	4.51	0.34	
174	SEQ ID NO:179	L328A	0.30	4.24	1.03	1.11	0.34	1.06	

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Please delete the paragraph beginning at page 147, paragraph [240] and replace with the following rewritten paragraph:

--[240] These data show even more convincingly that it is possible to tune Fc for Fc ligand specificity, often by using very subtle mutational differences. For example, the A330Y/I332E variant (SEQ ID NO:112) enhances binding to all FcγRs, particularly FcγRIIIa, as well as FcRn, while maintaining binding to C1q. However the A330L/I332E variant (SEQ ID NO:114) shows enhanced binding to FcγRI and FcγRIIIa, but has WT affinity for the FcγRII's. In contrast, mutations at L328 provide preferential

enhancement of the FcγRII's over FcγRI and FcγRIIIa. In the case of the L328E/I332E variant (SEQ ID NO:172), affinity for all FcγRII's is increased, whereas L328T/I332E (SEQ ID NO:176) provides a clear enhancement specificity profile of FcγRIIc > FcγRIIb > FcγRIIa. In contrast, L328A significantly enhances binding to FcγRIIa, but provides WT affinity for all other FcγR's including FcγRIIb and FcγRIIc. It is clear from these results that very subtle mutational differences can provide substantial differences in specificity. Accordingly, collections of Fc variants such as these will not only enable the generation of antibodies and Fc fusions that have effector function tailored for the desired outcome, but they also provide a unique set of reagents with which to experimentally investigate and characterize effector function biology.--

Please insert the enclosed 355-page text entitled "SEQUENCE LISTING" immediately preceding the claims.